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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
SCHMIDT, MARY M

ART UNIT	PAPER NUMBER
1635	19

DATE MAILED: 05/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/428,458	TASKEN ET AL.	
	Examiner	Art Unit	
	Mary M. Schmidt	1635	

-- The MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-45 and 47-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-45 and 47-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 October 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Objections

2. Claim 43 is missing a preposition before 'subject' in line 3.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 40-45 and 47-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for use of Rp-8-Br-cAMPS, Rp-8-Cl-CAMPS and Rp-8-Br-monobutyryl-cAMPs in pharmaceutical compositions and in methods of treatment of CVI, AIDS or HIV infection for the inhibition of PKA type I alpha, does not reasonably provide enablement for the use of the breath of claimed pharmaceutical compositions and methods of treatment of any immunosuppressive disease or the inhibition of any effects mediated by PKA type Ialpha isozyme as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Note that the instant 35 U.S.C. 112 rejection over the pharmaceutical composition claims 40-42 would be overcome by amendment of the claims to remove the language "pharmaceutical" from the preamble. Since the claims currently state a pharmaceutical composition, having implied administration to a whole organism for treatment purposes, the claims are included in the instant rejection.

Claim 40 is drawn to a pharmaceutical composition useful for treating an immunosuppressive disease comprising: (A) a pharmaceutically effective amount of a cAMP antagonist, wherein said cAMP antagonist is selected from the group consisting of Rp-8-Br-cAMPs, Rp-8-Br-monobutyryl-cAMPS, Rp-monobutyryl-cAMPS, Rp-8-(4-chlorophenyl-thio)-cAMPS and Rp-piperidino-cAMPS; and (B) a pharmaceutically acceptable adjuvant or filler.

Claim 41 states that the cAMP antagonist of claim 40 is Rp-8-Br-cAMPS. Claim 42 states wherein the immunosuppressive disease is selected from the group consisting of AIDS, HIV infection and CVI.

Claims 43 and 44 are drawn to methods of inhibiting the effects mediated b y PKA type Ialpha isozyme comprising administering to a subject in need of said inhibition, a pharmaceutical composition comprising (A) a pharmaceutically effective amount of a cAMP antagonist, wherein said cAMP antagonist is selected from the group consisting of Rp-8-Br-cAMPs, Rp-8-Br-monobutyryl-cAMPS, Rp-monobutyryl-cAMPS, Rp-8-(4-chlorophenyl-thio)-cAMPS and Rp-piperidino-cAMPS; and (B) a pharmaceutically acceptable adjuvant or filler. Claim 44 specifies that the cAMP antagonist is Rp-8-Br-cAMPS.

Claims 45, 47, 48 and 49 are drawn to a method of treating a subject afflicted with an immunosuppressive disease, comprising administering to said subject a pharmaceutical composition comprising: (A) a pharmaceutical effective amount of a cAMP antagonist sufficient to treat an immunosuppressive disease selected from the group consisting of AIDS, HIV infection and CVI, wherein said cAMP antagonist selectively or specifically abolishes the function of cAMP dependent protein kinase (PKA) type I alpha isozyme (Rialpha2C2); and (B) a pharmaceutically acceptable adjuvant or filler. Claim 47 states the method of claim 45, wherein said cAMP antagonist is a thio-substituted cAMP analog, wherein said thio-substituted cAMP analog is an equatorial diastereomer of 3',5'-cyclic adenosine monophosphorothioate (Rp-cAMPS), and wherein said thio-substituted cAMP analog binds to an Rialpha subunit of said isozyme and acts as a selective or specific antagonist of said isozyme. Claim 48 states the method of claim 47 wherein said cMAP antagonist is selected from the group consisting of Rp-8-Br-cAMPs, Rp-8-Br-monobutyryl-cAMPS, Rp-monobutyryl-cAMPS, Rp-8-(4-chlorophenyl-thio)-cAMPS and Rp-piperidino-cAMPS. Claim 49 states wherein the cAMP antagonist is selected from the group consisting of Rp-8-Br-cAMPS and Rp-8-Cl-cAMPS.

The specification as filed teaches the administration of Rp-8-Br-cAMPS, Rp-8-Cl-CAMPs and Rp-8-Br-monobutyryl-cAMPs for improvement in immunological conditions. However, the specification as filed does not teach use of the other claimed compounds Rp-monobutyryl-cAMPS, Rp-8-(4-chlorophenyl-thio)-cAMPS and Rp-piperidino-cAMPS, or any

other thio-substituted cAMP analog or an equatorial diastereomer of 3',5'-cyclic adenosine monophophorothioate (Rp-cAMPS).

The breath of the compounds is not considered enabled by the instant specification since the prior art taught the unpredictability of the use of cAMP antagonists. Note Gjertsen et al. (*The Journal of Biological Chemistry*, Vol. 270, No. 35, Issue of September 1, pp. 20599-20607, 1995) who taught that "[n]ovel (Rp)-cAMPs analogs differed widely in ability to antagonize cAMP activation of pure cAMP-dependent protein kinase I and II and to antagonize actions of cAMP.... These differences were related to different abilities of the analogs to stabilize the holoenzyme form relative to the dissociated form of cAMP kinase type I and II." (abstract) They further taught that "(Rp)-8-Br-cAMPS and (Rp)-8-Cl-cAMPS were the most potent cAMP antagonists for isolated type I kinase and for cells expressing mostly type I kinase.... It is proposed that (Rp)-Br-cAMPS or (Rp)-8-Cl-cAMPS should replace (Rp)-cAMPS as the first line cAMP antagonist, particularly for studies in cells expressing predominantly type I kinase." (Abstract) On page 20600, col. 2, they further stated (see results section, 'screening of (Rp)-cAMPS analogs for potential usefulness as cAMP antagonists') that (Rp)-8-cAMPS, (Rp)-8-Br-cAMPS, and (Rp)-8-Cl-cAMPS and (Rp)-8-chlorophenylthio-cAMPS all functioned as a cAMP analog. However, they further taught that "the following analogs were inactive or much less active in this respect: (Rp)-2-Cl-cAMPS, (Rp)-N6-butyryl-cAMPS, (Rp)-N6-phenyl-cAMPS, (Rp)-cGMPS, (Rp)-8-Br-cGMPS, (Rp)-8-Cl-cGMPS, (Rp)-8-chlorophenylthio-cGMPS, and (Rp)-8-aminobutylamino-cAMPS, (Rp)-8-Chloro-phenylthio-cAMPS...."

Therefore, since neither the prior art nor the specification as filed taught that other cAMP analogs, other than Rp-8-Br-cAMPS, Rp-8-Cl-CAMPs and Rp-8-Br-monobutyryl-cAMPs were able to have the claimed effects in a whole organism on immunological disorders, and since Gjertsen et al. taught that the cAMPS analogs are not all enabled for acting as cAMP analogs in a cell, then one of skill in the art would not have sufficient guidance in order to use the other claimed analogs for the claimed functions *in vivo*. The unpredictable factor is taught by Gjertsen et al., not all cAMP analogs are able to function to the same degree as cAMP. Thus, one skilled in the art would necessarily practice *de novo* "trial and error" experimentation to make and use cAMPS analogs other than Rp-8-Br-cAMPS, Rp-8-Cl-CAMPs and Rp-8-Br-monobutyryl-cAMPs having the *in vivo* functions of use in treatment of immunological disorders. The amount of experimentation is considered undue since one of skill in the art would have to develop without any guidance novel analogs that are able to function *in vivo* for the claimed purposes.

Claim Rejections - 35 USC § 102

5. Claims 40-42 are rejected under 35 U.S.C. 102(b) as being anticipated by Gjertsen et al. (J. of Biol. Chem. Vol. 170, No. 35, pp. 20599-607, 1995).

Claim 40 is drawn to a pharmaceutical composition useful for treating an immunosuppressive disease comprising:

(A) a pharmaceutically effective amount of a cAMP antagonist, wherein said antagonist is selected from the group consisting of Rp-8-Br-cAMPS, Rp-8-Br-monobutyryl-cAMPS, Rp-monobutyryl-cAMPS, Rp-8-(4-chlorophenyl-thio)-cAMPS and Rp-piperidino-cAMPS; and

(B) a pharmaceutically acceptable aduvant or filler.

Claim 41 is drawn to the pharmaceutical composition according to claim 40, wherein said cAMP antagonist is Rp-8-Br-cAMPs.

Claim 42 is drawn to the pharmaceutical composition according to the group consiting of AIDS, HIV infection and CVI.

Gjertsen et al. taught in the abstract (line 9) the use of (Rp)-Br-cAMPS . Gjertsen et al. also taught the limiation of use of a filler with the (Rp)-Br-cAMPS (on page 20600, col. B, results section, first para., line 9) at concentrations up to 0.5-1 mM. The liquid solvent used by Gjertsen et al. is within the meaning of "filler" provided in the instant specification on page 9, lines 1-3, that states "injection fluids" or "infusion fluids" are considered embraced by the invention.

Although Gjertsen et al. does not teach the limitation "pharmaceutically acceptable amount" of the cAMP antagonist, the concentrations they used (0.5-1mM) are equivalent to the concentrations used in the instant specification, Figure 3D, which shows use of 0-1000 10^{-6} M, or 0-1 mM, of Rp-8-Br-cAMPS used.

The functional language in the preamble of the claims, "useful for treating an immunosuppressive disease" is merely a recitation of intended use of the claimed composition.

MPEP 2111.02 states that "[a]ny terminology in the preamble that limits the structure of the claimed invention must be treated as a claim limitation. If the body of a claim fully and intrinsically sets forth all of the limiations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitation, then the preamble is not considered a limiation and is of no significance to claim construction.... "where a patentee defines a structually complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention, the preamble is not a claim limitation"... preamble is not a limiation where claim is directed to a product and the preamble merely recites a property inherent in an old product defined by the remainder of the claim...." In the instant case, the use of the otherwise known composition for treatment of an immunosuppressive disease, does not alter the structure of the cAMP antagonists claimed. As such, the functional use language in the preamble is given no weight in the prior art rejection.

6. Claims 40-44 are rejected under 35 U.S.C. 102(e) as being anticipated by Cho-Chung et al. (U.S. Patent 5,843,916).

Claim 40 is drawn to a pharmaceutical composition useful for treating an immunosuppressive disease comprising:

(A) a pharmaceutically effective amount of a cAMP antagonist, wherein said antagonist is selected from the group consisting of Rp-8-Br-cAMPS, Rp-8-Br-monobutyryl-cAMPS, Rp-monobutyryl-cAMPS, Rp-8-(4-chlorophenyl-thio)-cAMPS and Rp-piperidino-cAMPS; and

(B) a pharmaceutically acceptable aduvant or filler.

Claim 41 is drawn to the pharmaceutical composition according to claim 40, wherein said cAMP antagonist is Rp-8-Br-cAMPs.

Claim 42 is drawn to the pharmaceutical composition according to the group consiting of AIDS, HIV infection and CVI.

Claim 43 is drawn to a method of inhibiting the effects mediated by PKA type Ialpha isozyme comprising administering to a subject in need of said inhibition, a pharmaceutical composition comprising:

(A) a pharmaceutically effective amount of a cAMP antagonist, wherein said cAMP antagonist is selected frm the group consisting of Rp-8-Br-cAMPS, Rp-8-Br-monobutyryl-cAMPS, Rp-monobutyryl-cAMPS, Rp-8-(4-chlorophenyl-thio)-cAMPS and Rp-piperidino-cAMPS; and

(B) a pharmaceutically acceptable aduvant or filler.

Claim 44 is drawn to the method according to Claim 43, wherein said cAMP antagonist is Rp-8-Br-cAMPS.

Cho-Chung et al. taught in col. 6, lines 61-65, "phosphorothioate derivatives of 8-halo-cAMP, preferably 8-Cl-cAMP and 8-Br-cAMP" They further taught that said compositions may be contacted with cells to inhibit cell proliferation (col. 7, lines 15-35) and that they may be made as a pharmaceutical composition.

The functional language in the preamble of claims 40-42, "useful for treating an immunosuppressive disease" is merely a recitation of intended use of the claimed composition. MPEP 2111.02 states that "[a]ny terminology in the preamble that limits the structure of the claimed invention must be treated as a claim limitation. If the body of a claim fully and intrinsically sets forth all of the limiations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitation, then the preamble is not considered a limiation and is of no significance to claim construction.... "where a patentee defines a structually complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention, the preamble is not a claim limitation"... preamble is not a limiation where claim is directed to a product and the preamble merely recites a property inherent in an old product defined by the remainder of the claim...." In the instant case, the use of the otherwise known composition for treatment of an immunosuppressive disease, does not alter the structure of the cAMP antagonists claimed. As such, the functional use language in the preamble is given no weight in the prior art rejection.

7. Claims 45 and 47-49 are considered free of the prior art since the prior art cited above did teach administration of the claimed compounds to a subject but did not teach nor fairly suggest methods of treatment of an immunosuppressive disorder as claimed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Inquiries relating to the status of this application may also be directed to *Katrina Turner*, whose telephone number is (703) 305-3413.

JOHN L. LeGUYADER
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M. M. Schmidt
May 1, 2003